Please add the following new claim.

22. The method of claim 1 wherein the ability of the agent to increase MLC1 phosphorylation is assessed in vitro in myofilament or skinned muscle fibers.

REMARKS

Claims 1-21 are pending in the instant application. Claims 4-11, 13 and 15 have been withdrawn from consideration by the Examiner and subsequently canceled without prejudice by Applicants in this amendment. Claims 1-3, 12, 4 and 16-21 have been rejected. Claims 1, 2 and 12 have been amended. New claim 22 has been added. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Finality of Restriction Requirement

The Examiner has made final the Restriction Requirement mailed May 31, 2002. Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have canceled non-elected claims 4-11, 13 and 15, without prejudice. However, in light of the finality of this Restriction Requirement,

Applicants reserve the right to file a divisional application to the canceled subject matter.

II. Rejection of Claims 1-3, 12, 14 and 16-21 under 35 U.S.C. § 112, second paragraph

Claims 1-3, 12, 14 and 16-21 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner suggests that claim 1 and claims which depend therefrom are indefinite because the claims fail to set forth any positive limitation regarding how one would determine if the agent is in fact a muscle protecting agent. The Examiner also suggests that recitation of "muscle protective agent" is vague and indefinite because it is unclear what is included or excluded by the term.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 1 to clarify that by muscle protective agent it is meant an agent that inhibits damage to cardiac and skeletal muscle. Further, Applicants have amended the claim to include the positive limitation that the ability of

the agent to increase MLC1 phosphorylation is indicative of the agent inhibiting damage to cardiac and skeletal muscles. Support for these amendments can be found in the specification at page 12, lines 16-27.

In addition, the Examiner suggests that claim 1 and its dependents are indefinite for recitation of MLC1 without first writing out the full term. Accordingly, Applicants have amended claim 1 to include the full term of myosin light chain 1. Support for this amendment is provided in the specification at page 1, lines 8-10.

The Examiner suggests that claim 2 is confusing for reciting "or" in lines 4 and 5 because it is unclear which terms are intended to be in the alternative. Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 2 to delete the alternative language of the phrase "or in myofilament or skinned muscle fibers" and represented this subject matter separately in new claim 22.

The Examiner suggests that claim 12 is vague and indefinite because the claim fails to set forth any positive limitation regarding how one would determine if the agent is in fact a therapeutic target or muscle protecting agent. Claim 12 is also

suggested to be indefinite because it is unclear what constitutes "acting on MLC1 phosphorylation".

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 12 to provide a positive limitation with respect to how one would determine that the identified kinase or phosphatase is a therapeutic target for an agent which inhibits damage to cardiac or skeletal muscle. Support for this amendment can be found in the specification at page 16, lines 19-24. Further, Applicants have replaced the phrase "act on MLC1 phosphorylation" with the phrase "modulate MLC1 phosphorylation status" in accordance with teachings in the specification at page 15, lines 11-19.

Claim 14 is suggested to be vague and confusing for reciting "IN sequence extraction" because the phrase is not adequately defined by the claim language or specification. Applicants respectfully traverse this rejection. Contrary to the Examiner's suggestion, the "IN sequence extraction" method is described in explicit detail in Example 2 beginning at page 18 of the specification. Thus, what is meant by this phrase is quite clear to one skilled in the art when read in light of the teachings of the specification as required by MPEP § 2173 and amendment to render claim 14 more definite is not required.

Withdrawal of these rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested in light of the amendments to the claims and the above arguments.

III. Rejection of Claims 1-3, 12, 14 and 16-21 under 35 U.S.C. § 103(a)

Claims 1-3, 12, 14 and 16-21 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kaibuchi et al. (U.S. Patent 5,906,819). The Examiner suggests that Kaibuchi et al. teaches methods for screening materials that inhibit Rho kinase activity. Further, the Examiner suggests that Kaibuchi teaches that Rho kinase phosphorylates MLC in cells and that identified agents which inhibit Rho kinase can be used to treat various circulatory system diseases. The Examiner has acknowledged that Kaibuchi does not teach methods wherein MLC is obtained from a biological sample using IN sequence extraction nor specific residues at which phosphorylation occurs. However, the Examiner suggests that the method for producing or obtaining MLC does not appear to structurally alter the MLC and location of the phosphorylation sites is inherent to the disclosed methods. Further, the Examiner suggests that one of ordinary skill in the

art would have been motivated to practice the methods of Kaibuchi with a reasonable expectation of identifying muscle protective agents.

Claim 1 has also been rejected under 35 U.S.C. § 103(a) as being unpatentable over De Lanorelle (WO 97/26268). The Examiner has acknowledged that De Lanorelle does not teach a method for identifying a muscle protective agent by assessing the ability of an agent to increase MLC1 phosphorylation. However, the Examiner suggests that at the time of the claimed invention, it would have been within the purview of one of ordinary skill in the art to do so since De Lanorelle specifically teaches that increasing MLC phosphorylation protects muscle cells from damage. Further, the Examiner suggests that one of ordinary skill in the art would have been motivated by De Lanorelle to reasonably expect agents which increase MLC phosphorylation to also be muscle protective agents.

Applicants respectfully traverse these rejections.

At the outset, it is respectfully pointed out that the myosin light chain taught in Kaibuchi and De Lanorelle is the regulatory light chain of smooth muscle referred to by those skilled in the art as MLC20, not myosin light chain 1 ("MLC1") as claimed in the present invention. See, for example column 15 and

Example 8 of Kaibuchi and the entire teachings of De Lanorelle referring to smooth muscle. MLC20 of smooth muscle and MLC1 are distinctly different proteins with different structures, properties and characteristics. For example, Kaibuchi teaches that their "MLC" is phosphorylated by myosin light chain (MLC) kinase (see example 8 and column 15, lines 40-41). In contrast, as taught in the instant application, phosphorylation of MLC1 by MLC kinase can only be achieved *in vitro* in the presence of ATPγS and not in the presence of [32P]-γATP and therefore not in vivo. Also see references AA and AC submitted with IDS.

Also see attached hereto a comparison of the amino acid sequences of MLC1 and MLC20 showing vast differences in amino acid sequence as well as differences in sites of phosphorylation (indicated by circles). As shown in this attachment, MLC20 as 7 serines and 11 threonines while MLC1 as 5 serines and 11 threonines. There is no overlap in terms of phosphorylation. Further, the single corresponding serine of MLC20 and MLC1 is only phosphorylated in MLC20, not MLC1here is no overlap

Thus, the teachings of Kaibuchi and De Lanorelle are not relevant to the instant claimed invention and in no way render obvious the instant claimed invention relating to MLC1 phosphorylation.

Withdrawal of these rejections under 35 U.S.C. § 103(a) is therefore respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto, is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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Date: **February 21, 2003**

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 4-11, 13 and 15 have been canceled without prejudice.

Claims 1, 2 and 12 have been amended as follows:

1. (amended) A method for identifying ~~a muscle protective~~ an agent which inhibits damage to cardiac and skeletal muscle comprising assessing the ability of a potential muscle protective agent to increase myosin light chain 1 (MLC1) phosphorylation wherein an increase in MLC1 phosphorylation by the agent is indicative of the agent inhibiting damage to cardiac and skeletal muscle.

2. (amended) The method of claim 1 wherein the ability of the ~~potential muscle protective~~ agent to increase MLC1 phosphorylation is assessed in vitro in purified myosin, purified myosin light chain 1, or purified isoforms thereof~~, or in myofilament or skinned muscle fibers~~.

12. (amended) A method for identifying new therapeutic targets ~~as muscle protective~~ for agents which inhibit damage to cardiac and skeletal muscle comprising identifying kinases or phosphatases that ~~act on~~ modulate MLC1 phosphorylation status, wherein modulation of MLC1 phosphorylation status by the

identified kinase or phosphatase is indicative of the identified kinase or phosphatase being a therapeutic target for an agent which inhibits damage to cardiac or skeletal muscle.